

11. (Amended) The composition of claim [2 or] 9 wherein the antibody is a scFv antibody.

12. (Amended) An isolated and purified polypeptide comprising at least a portion of a polypeptide that specifically binds CD38 and at least a portion of a polypeptide that specifically binds DNA, wherein the polypeptide which specifically binds CD38 is an antibody.

Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 3, 9, and 11-12 are amended, and claims 2, 14 and 16 are canceled. Claims 1, 3-13, 15, and 17-18 are now pending in this application. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation application of the present application.

Amended claim 1 is supported by originally-filed claims 1-2.

Amended claims 3, 9 and 11-12 are supported by originally-filed claims 3, 9 and 11-12, respectively.

The 35 U.S.C. § 103(a) Rejection

The Examiner rejected claims 1-13 and 17-18 under 35 U.S.C. § 103(a) as being unpatentable over Marasco et al. (WO 95/22618) in view of Goldmacher et al. (Blood, 84:3017 (1994)), Ellis et al. (J. Immunol., 1515:925 (1995)), and Donovan et al. (Blood, 90:396 (1997)). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Marasco et al. disclose a nucleic acid delivery system for gene therapy (abstract). The system contains a fusion protein having a targeting moiety, such as an antibody, and a nucleic acid binding moiety, such as protamine, and a nucleic acid sequence, e.g., one which encodes a toxin gene, bound to the nucleic acid binding moiety of the fusion protein (page 6, lines 6-16 and page 9, lines 21-29). It is disclosed that the targeting moiety may be one which binds a particular cell surface receptor such as one on a tumor cell (page 13, lines 1-6). Marasco et al. report the

preparation of an anti-gp120 antibody-protamine fusion protein (pages 24-29), the binding of the fusion protein to gp120 (pages 29-31), and the formation of complexes of the fusion protein and DNA (pages 31-33). It is also disclosed that HIV-1 infected Jurkat cells were incubated with the fusion protein, an expression cassette containing a CMV promoter linked to a toxin gene (the *Pseudomonas* exotoxin A gene), or complexes of the expression cassette and the fusion protein (page 36). Cells incubated with the complexes had a significant decrease in cell viability (Figure 10, lanes c-e).

Marasco et al. do not teach anti-CD38 antibodies, e.g., anti-CD38 scFv antibodies, a fact conceded by the Examiner. Moreover, Marasco et al. do not disclose or suggest the use of a cell- or tissue-specific transcriptional unit linked to a DNA encoding a cytotoxic agent.

Goldmacher et al. prepared an immunotoxin having chemically-modified ricin (in which the galactose binding sites on the B chain were blocked) conjugated to an anti-CD38 monoclonal antibody (HB7) (abstract). Goldmacher et al. disclose that the immunotoxin exhibited a four to six log CD38⁺ tumor cell line kill and inhibited protein synthesis in bone marrow mononuclear cells from multiple myeloma patients, but had no toxicity for normal resting peripheral blood lymphocytes at concentrations up to 1 nmol/L and showed only a low level of toxicity for normal bone marrow precursors (abstract and Figures). The authors conclude that the HB7-blocked ricin immunoconjugate, with its potent specific cytotoxicity for tumor cells and low cytotoxicity for normal cells, may have clinical utility for the *in vivo* or *in vitro* purging of human multiple myeloma cells (page 301).

Goldmacher et al. do not disclose or suggest a fusion polypeptide comprising an anti-CD38 antibody and a polypeptide that specifically binds DNA.

Ellis et al. prepared derivatives of a high affinity monoclonal antibody against CD38 (AT13-5) that can engage human effector mechanisms and have reduced immunogenicity (abstract). One derivative was a CDR-grafted humanized IgG1, and the other was a chimeric FabFc₂ (mouse Fab crosslinked to two human γ_1 Fc). The authors disclose that both the humanized IgG1 and FabFc₂ directed antibody-dependent cellular cytotoxicity against CD38⁺ cell lines (abstract). Ellis et al. indicate that lytic anti-CD38 antibodies have therapeutic potential for multiple myeloma as well as other disorders of plasma cells or cells which express CD38 (page 935).

Ellis et al. do not disclose or suggest a fusion polypeptide comprising an anti-CD38 antibody and a polypeptide that specifically binds DNA.

With respect to Donovan et al., the Examiner is requested to consider the enclosed Rule 132 Declaration executed by Anne Koch. In the Rule 132 Declaration, Ms. Koch, a Knowledge Analyst employed by the undersigned attorney for Applicant, determined that the Donovan et al. abstract was not available to the public before November 1997. Because this date is less than one year prior to the effective filing date of the present application (i.e., June 5, 1998), Donovan et al. is at best available as prior art under 35 U.S.C. § 102(a). However, the named inventors of the present application are the same as the authors named on the Donovan et al. abstract, i.e., Kathleen A. Donovan and John A. Lust. In the absence of a statutory bar, a disclosure by the inventors of their later-filed invention is not prior art. In re Katz, 215 U.S.P.Q. 14 (C.C.P.A. 1982). Accordingly, Donovan et al. is not available as prior art to the present application.

The Examiner asserts that Marasco et al. provide motivation for i) targeting tumors with an anti-CD38 antibody, either a Fab, scFv or humanized antibody, by teaching that the use of the disclosed DNA-immunoconjugates allows for the delivery of cytotoxic genes to target cells such as tumors without the immunogenicity/toxicity problems associated with traditional immunotoxins, and ii) choosing antibodies which target cell surface receptors which are present in large amounts on certain tumors. The Examiner also asserts that, based on the successful use of the CD38 antibodies taught by Donovan et al. and Ellis et al. to target CD38+ cells, the skilled artisan would have had a reasonable expectation of success in making and using a composition comprising an anti-CD38 antibody linked to protamine and complexed with a plasmid encoding an exotoxin. The Examiner thus concludes that it would have been *prima facie* obvious to the skilled artisan to use the anti-CD38 antibody taught by Goldmacher et al., Ellis et al., or Donovan et al. in the compositions and methods taught by Marasco et al.

Nevertheless, the combination of the cited art does not disclose or suggest Applicant's invention. Marasco et al. generally disclose the use of a fusion protein having a targeting moiety and a nucleic acid binding moiety to deliver a negative potentiator gene, such as a toxin gene, to specific cells. To eliminate antigen-specific cells, the toxin gene must be taken up and expressed by the cell. Goldmacher et al. disclose the use of an immunotoxin in which an anti-CD38 monoclonal antibody is used to target the immunotoxin to CD38⁺ cells. To eliminate those

CD38⁺ cells, the immunotoxin must be taken up by the cell and the chemically-modified ricin must localize to and inactivate ribosomes. Ellis et al. disclose an anti-CD38 CDR-grafted humanized IgG1 and a chimeric anti-CD38 FabFc₂ which engage human effector mechanisms to lyse CD38⁺ cells.

Thus, each of the three available references proposes a different means to target and eliminate antigen-specific cells and there is no direction in those references to prepare Applicant's compositions or practice Applicant's methods. In particular, none of the available cited art discloses or suggests a composition comprising a polypeptide comprising an antibody which specifically binds CD38 or a portion thereof linked to a polypeptide which specifically binds DNA or a portion thereof and a DNA sequence encoding a cytotoxic agent which is operably linked to a cell- or tissue-specific transcriptional unit or the use of such a composition (claims 1, 3-11, and 13). Moreover, none of the available cited art discloses or suggests an isolated and purified polypeptide comprising at least a portion of an antibody that specifically binds CD38 and at least a portion of a polypeptide that specifically binds DNA, or a recombinantly produced single chain fusion polypeptide comprising the Fv region of the light and the heavy chain of a CD38 specific antibody and a DNA binding polypeptide, wherein the Fv region and the DNA binding polypeptide are recombinantly fused to form a single chain polypeptide that specifically binds CD38⁺ cells (claims 12 and 17-18).

Accordingly, withdrawal of the § 103 rejection is respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Rejections

The Examiner rejected claims 1, 4-8, 10, 12-13, and 15 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to claim 1 renders this rejection moot.

The Examiner also rejected claims 1-13, 15 and 18 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Specifically, the Examiner asserts that 1) the specification fails to provide an enabling disclosure for making a fusion polypeptide which includes a CD38 binding peptide which is not an antibody; 2) the specification fails to provide an enabling disclosure for targeting CD38⁺ cells, including multiple myeloma cells *in vivo*, using the fusion polypeptide alone or complexed *in vitro* with plasmid DNA; 3) the specification fails to provide sufficient guidance for routes and sites of administration, dosages of the complexed vectors, and the level of toxin gene expression required to effectively treat or inhibit multiple myeloma; and 4) the *in vivo* use of immunotoxins as of the effective date of the application was unpredictable due to their immunogenicity, toxicity, and lack of specificity. To support basis 4) of the rejection, the Examiner cites Maloney et al. (Sem. in Hematol., 36:30 (1999)); Deonarain (Exp. Op. Ther. Patents, 8:53 (1998)); and Miller et al. (FASEB, 9:198 (1995)).

The amendment to claim 1 renders basis 1) of the rejection moot.

With respect to basis 3), the Examiner is requested to consider Marasco et al., a reference cited against the claims under § 103(a), which is presumed to be enabling (M.P.E.P. 2121). Marasco et al. disclose routes of administration and dosages for a fusion protein having a targeting moiety and a nucleic acid binding moiety and a nucleic acid sequence, e.g., one which encodes a toxin gene (see pages 21-23). Marasco et al. also disclose that for many toxins, only a few molecules per cell may result in cell death (page 12). Thus, a single copy of DNA encoding a toxin gene, if expressed in a cell, is likely sufficient to induce cell death.

Moreover, the dosages and routes of administration of antibodies including anti-CD38 antibodies are well known to the art. See, for example, page 117 of Garnier et al. (Recent Results in Cancer Res., 159:112 (2002), a copy of which is included herewith) which refers to articles in 1995 and 1998 in which patients who developed a B cell lymphoma after kidney transplant were infused with anti-CD38 antibodies at 12 mg/kg. Notably, those patients “were put in complete remission” (page 117).

Further, the Examiner is respectfully reminded that the selection of dosages, dosage forms, dosage schedules and routes of administration for a particular agent is well within the skill of the art worker (e.g., see In re Johnson, 282 F.2d 370, 127 U.S.P.Q. 216 C.C.P.A. 1960).

Applicant need not teach what is well-known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986).

Regarding basis 2), the Examiner is respectfully reminded that the test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the application coupled with information known in the art without undue experimentation.

United States v. Telectronics Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

Applicant's specification discloses that an anti-CD38 scFv polypeptide was prepared and found to bind to CD38+ cells (Figure 2). Moreover, the bound anti-CD38 scFv polypeptide was internalized (Figure 3). And, as reported in Maloney et al., an anti-CD38 scFv-protamine fusion formed complexes with DNA (page 33 in Maloney et al.).

Thus, given the disclosure in Marasco et al., the *in vivo* efficacy of anti-CD38 antibodies (Garnier et al.), and the Examiner's concession that based on the successful use of the CD38 antibodies taught by Ellis et al. to target CD38+ cells, the skilled artisan would have had a reasonable expectation of success in making and using a composition comprising an anti-CD38 antibody linked to protamine and complexed with a plasmid encoding an exotoxin (page 12 of the Office Action), it is respectfully submitted that one of ordinary skill in the art in possession of Applicant's specification would reasonably predict that complexes of a fusion of an anti-CD38 antibody and a DNA binding protein with DNA encoding a toxin gene, would target and inhibit CD38⁺ cells *in vitro* or *in vivo*.

In this regard, the Examiner is also requested to consider the Rule 132 Declaration enclosed herewith executed by Dr. John A. Lust, a coinventor of the present application. In that Declaration, Dr. Lust states that his laboratory has shown that complexes of a fusion polypeptide comprising an anti-CD38 antibody and a DNA binding protein and plasmid DNA, bound to CD38⁺ cells, and that the complexes were internalized (paragraph 3 of the Declaration). Moreover, based on such *in vitro* data, Dr. Lust concludes that those complexes would bind to and be internalized by CD38⁺ cells *in vivo*.

The unpredictability of immunotoxins (basis 4 of the rejection), according to the Examiner, is related to their toxicity, immunogenicity and lack of specificity. The toxicity of immunotoxins is related to the presence of the toxin, while the immunogenicity may be due to

the toxin or the antibody portion of the immunotoxin. The specificity of an immunotoxin is related to the antibody employed in the immunotoxin.

Nevertheless, the Examiner is respectfully requested to consider that the composition recited in claim 1 is not an immunotoxin, i.e., a toxin covalently linked to an antibody molecule, but instead comprises a toxic gene and a fusion of an anti-CD38 antibody and a nucleic acid binding moiety. Accordingly, the Examiner is requested to note that two of the alleged unpredictable features of immunotoxins, i.e., toxicity and immunogenicity, are addressed by the present invention as complexes of a toxic gene and a fusion of an anti-CD38 antibody and a nucleic acid binding moiety reduce the immunogenicity and toxicity of those complexes relative to immunotoxins.

The Examiner asserts that Maloney et al. teach that the administration of an immunotoxin comprising an anti-CD38 antibody to patients with myeloma resulted in the generation of human anti-mouse antibodies (HAMA) and toxicity induced episodes of blindness in the absence of an effect on the myeloma (page 7 of the Office Action). However, Maloney et al. point out that the use of genetically and chemically engineered antibodies can ameliorate HAMA responses (page 31), and they note that only ¼ of patients treated with genetically or chemically engineered anti-CD38 antibodies developed a HAMA response (Table 2). The blindness, which was observed in one patient who was first treated with engineered anti-CD38 antibodies and then with a mouse Fab₂ human Fc-saporin immunotoxin, was temporary. And as for the alleged absence of any anti-myeloma effect, it is unclear whether the reported study was intended to measure such an end point, although the authors disclose that minor responses were observed (page 31).

The Examiner asserts that Deonarain teaches that one of the main obstacles to successful gene therapy is "...the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that "...even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" and that Miller et al. concurs with Deonarain by teaching that the development of surface targeting had been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since "attainment of one usually compromises the other" (overlapping sentence at pages 7-8 of the Office Action). The Examiner concludes that

targeted delivery of nucleic acids to specific cells or tissues *in vivo* is considered highly unpredictable (page 7 of the Office Action).

The quotes in Deonarian chosen by the Examiner appear as introductory remarks and so are misleading. The majority of the article is directed to discussing the merits of ligand-targeted receptor mediated endocytosis (RME) with receptor-mediated polyplexes. Deonarian discloses that many ligand/receptor systems are under investigation “each one demonstrating successful gene transfer with a higher level of specificity than viruses can offer” (page 53).

Miller et al. describe the use of genetically engineered viral glycoproteins to confer specific binding affinity as “a promising approach” (page 191). Miller et al. refer to three reports of modifications to a retroviral glycoprotein, two of which led to an altered cell tropism (page 192). Miller et al. also refer to other modifications leading to an altered cell tropism including the preparation of retroviral-ligand conjugates (page 192). Of three reports directed to this type of targeting approach, Miller et al. note that two were successful and the third showed at least partial success. Another approach, liposome vectors with a targeting moiety, e.g., viral proteins or antibodies, had been shown to increase gene delivery according to Miller et al.

Hence, none of the cited references provide any evidence that the use of antibody-based therapies is wholly unpredictable.

Moreover, with respect to the use of antibodies, the art clearly recognizes that antibodies to a particular antigen are useful to specifically target that antigen, e.g., see Goldmacher et al., Ellis et al., and WO 96/16990, and that it is reasonably predictable that antibodies may be employed to treat neoplastic disease, e.g., anti-CD20 antibodies currently employed to treat B cell malignancies include Rituximab™, Zevalin™, and Bexxar™; Leonard et al. (Sem. Oncol., 29:81 (2002)); Cremer et al. (Blood, 96:298 (2000)); and Garnier et al. (Recent Results in Cancer Res., 159:112 (2002)). For example, Garnier et al. report that “[t]he efficacy and safety of anti-B-cell monoclonal antibodies (mAbs) in transplant patients have been proven with different antibodies such as anti-CD21/CD24 mAb, anti-CD38 mAb and anti-CD20 mAb” (page 113). Leonard et al. disclose immunotherapy of non-Hodgkin’s lymphoma with an anti-CD22 mAb, and Cremer et al. report the use of anti-CD20 antibodies to treat patients with multiple myeloma after high dose therapy and peripheral blood stem cell transplantation.

Further, as noted by Maloney et al., complexes of a gene encoding a toxin and a fusion polypeptide having a targeting moiety and a nucleic acid binding moiety result in “targeted expression of a toxin gene” (page 33) and those complexes have reduced immunogenicity as they lack the toxin (page 33).

In fact, the Maloney et al. article emphasizes that the data so far relating to the use of immunotherapy is quite positive, e.g., “[m]onoclonal antibody therapy has emerged as a viable option for patients with lymphoma and some leukemias” (page 30), and anti-CD20 antibodies have been successfully used to treat patients with follicular lymphoma (page 30) and that anti-CD40 antibody treatment prolonged survival in *bcl-1* lymphoma (page 31). Maloney et al. notes that at least six antigens are targets for immunotherapy of multiple myeloma, including CD38 (Table 1), and that clinical trials with antibodies against those targets are ongoing (page 30).

Finally, the Examiner is also requested to consider the Rule 132 Declaration executed by Dr. Lust. In that Declaration, Dr. Lust states that antibodies are recognized as one, if not the best, current approach for targeting *in vivo* (paragraph 5 of the Declaration), and that the predictability of immunotherapy has been shown for antibodies including anti-CD38 antibodies (paragraph 4 of the Declaration).

Therefore, Applicant’s specification is fully enabling.

Hence, withdrawal of the § 112(1) rejection is appropriate and is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant’s attorney (612-373-6959) to facilitate prosecution of this application.

AMENDMENT AND RESPONSE UNDER 37 CFR § 1.111

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Respectfully submitted,

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By their Representatives,

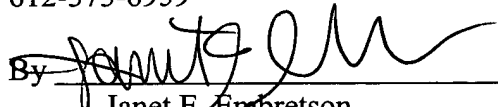
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